

## The Genetics Program at Stanford University

The opportunity to establish a program of genetics oriented to medicine at Stanford has resulted from the move of the Medical School from San Francisco to the University campus at Palo Alto. The new academic setting of the School symbolizes the determination of its leadership and staff to strengthen Stanford's position in training and research in the scientific foundations of medicine. The educational program is designed to stimulate academic and research interests of the undergraduate medical students; much effort will be spent on research and advanced training for Ph.D. candidates and postdoctoral fellows. The recent appointments of Arthur Kornberg as Professor and Executive in Biochemistry, with his accompanying staff, and of Joshua Lederberg in the same positions in Genetics, illustrates the dedication to scientific excellence which characterizes the contemporary Stanford environment.

Plans for a Department of Genetics did not materialize until after contracts had been let for the construction of the Medical Center, stage one, so there was no explicit provision for it. However, the Departments of Pharmacology and Biochemistry have made available a total of about 1800 feet of laboratory and office space to house Dr. Lederberg's unit in microbial genetics. Equally important will be his sharing in their general facilities and services needed for the work (e.g. cold rooms, sterilizers, some special apparatus). This should make for an especially congenial working relationship with some of the intellectually and materially best equipped biochemical research teams in the United States. It is noteworthy that Professors Kornberg (Biochemistry), Kaplan (Radiology), Goldstein (Pharmacology) and Alway (then Pediatrics, now Dean) personally played especially active roles in laying the groundwork for the foundation of the Genetics Department. This may be taken as the most trustworthy evidence of our concern for establishing a secure place for genetics in the medical research and training program.

For the other units in genetics, an area of about 4,000 square feet has been set aside on the ground floor of the same building. The Medical School is planning a substantial addition during the next few years in which there will be final consolidation of the Genetics Laboratories.

Genetics has had a long tradition at Stanford in the Medical School (e.g. Professor Danforth in Anatomy) and elsewhere (e.g. the now classic studies of Beadle and Tatum in Biology), and there will continue to be considerable activity in several departments.

Stanford is not trying to "cover" every possible facet of genetics, for example there is no direct representation of work in *Drosophila*. On the other hand this faculty can furnish a unique concentration of interests and skills on the problems of cellular determination and its interrelation with nucleic acid chemistry. Fortunately there are also many congenial colleagues at Berkeley and Davis who reinforce and complement the interests of the Stanford faculty. The universities have recently made new agreements to help graduate students take better advantage of the academic pool. Finally, Professor van Niel's summer course in microbiology is a unique training opportunity; for many years it has attracted some of the best

graduate students in microbial genetics throughout the country.

The final complexion of the Genetics Department will depend on the choice of its staff. This is planned to comprise the additional appointments "X" and "Y" in transplantation genetics and human genetics respectively.

Professor Lederberg, with his wife and other associates and students, plans to continue to work mainly on the genetics of microorganisms with special emphasis on (1) the characterization of the sexual determinant 'F' in *E. coli* in its alternative nuclear and extra nuclear phases; (2) the mating reaction by biochemical and cytogenetic analysis; (3) intergeneric hybridization, *Escherichia* X *Salmonella* and (?) *Escherichia* X *Pseudomonas*; (4) biochemical genetics (fine structure analysis) of mutations affecting enzymes for fermentation of various sugars; and (5) search for additional mechanisms of recombination, especially DNA-mediated transduction. Item (5) is urgently needed for a direct attack on the role of extra-nuclear information in cellular heredity, now a leading question in the controversies of geneticists and embryologists. He has an immediate interest in two other programs which will require extensive collaboration: the design of synthetic macromolecules capable of some degree of auto-replication, and the genetic mechanism of antibody formation. The second of these is a special interest of Dr. Nossal, coming as a research associate from Dr. Burnet's laboratory in Melbourne, and with whom Dr. Lederberg had already collaborated during a Fulbright visit in 1957. Finally, he is looking forward to association with Professor Kornberg's attack on the problem of *in vitro* synthesis of DNA, to provide whatever is possible from the standpoint of genetic analysis. Kornberg's associate Dr. A. D. Kaiser, has already made an exciting discovery of the transduction of Gal markers by lambda disrupted so that its DNA is accessible to DNase, and it would seem profitable to tie in with the Lederbergs' longstanding interest in the genetics of lambda transduction.

The expectation for Professor "X" and Dr. Herzenberg is a program that might be called "histogenetics": the genetics of tissue cells, which can be attacked with the methods either of transplantation or of tissue culture. The methodology of microbial genetics has already impressed a number of workers (e.g. T. Puck, George Klein, N. A. Mitchison) with the possibility of systematic genetic study of clones of mammalian tissue cells. The aim of such an approach is not to furnish another 'microorganism' (which may be rather more difficult to handle than *E. coli*) but to apply factorial analysis to hitherto elusive problems of the genetic basis of differentiation -- in normal development, in the immune response and acquired tolerance, and in the initiation of cancer. The advantages of organizing such a program within conversational distance of microbial genetics are obvious. In many respects, the immune response may be the most amenable aspect of differentiation owing to the extreme specificity of the induced cell type. Its genetic analysis might be expected to proceed by two main steps: (1) its basis in cellular heredity through vegetative reproduction, encompassing issues similar to that of induction versus selection in bacterial drug resistance, and (2) more hopefully, the establishment of procedures for recombination viz. parasexuality, transduction or microglial transplantation which can lead

to more precise localization of genetic functions in intracellular organelles.

The role of Professor "Y" might be to bridge the gap between these experimental studies on microbes and laboratory animals, on one side, and clinical studies on man, on the other. Sound work in human genetics today is impossible without a sound grasp of advanced biometrical methods to retrospectively exploit the large scale genetic 'experiments' of the human population. Ideally, this person should be, at the same time, a sound biometrician and an experimentalist dealing with human material along lines material to the other programs. The study of human blood factors perhaps will furnish the most apt area for such a program; one can point to contemporary studies of chemical polymorphism in human hemoglobins, chimerism in dizygotic twins, and mutation of serotype in the developing erythron as illustrations of quasi-experimental approaches to human genetics. Ultimately there is the prospect of analysis of human genotypes through somatic cells in culture, though it is difficult to justify bypassing experimentally more suitable material such as in cologenic lines of mice for the foundational work.

The Genetics Department is construed as a basic science department; its members will hope to advise, but not undertake primary responsibility for, clinical functions such as counseling or diagnosis and treatment of genetic diseases. There is a tacit understanding that an active clinical genetics program will be undertaken in one or more clinical departments, very likely Pediatrics and Medicine. Dr. Ruth T. Gross, Associate Professor of Pediatrics is already involved in her own research with genetic factors in hemolytic anemia of the newborn. Plans for the recruitment of additional staff for a clinical genetics program, presumably involving joint affiliation with Genetics, are being formulated in consultation with the newly appointed head of the Pediatrics Department, Dr. Norman Kretchmer.

This discussion does not do justice to the values expected from other departments in the Medical School. For example, Professor Henry Kaplan of the Department of Radiology leads a most energetic program on the cellular origins of tumor clones in mice and on the immunological interactions of graft and host -- the ready presence of a substantial colony of several lines of inbred mice and of a number of tumors will greatly facilitate the orderly development of the program for Dr. Herzenberg and Professor "X". Two postdoctoral fellows of outstanding qualifications have already been recruited on the premise of joint sponsorship by Drs. Kaplan and Lederberg. Dr. Lederberg has also established close connections with the Biology Department which has an active graduate program in genetics (Perkins, Yanofsky) and developmental biology (Grobstein, Twitty) and in which he holds a courtesy appointment. His research is temporarily housed in the Biophysics Laboratory pending the completion of the Medical Center. Studies there which are of great interest to genetics include radiobiology (concerned with very long as well as short wave lengths), electron-resonance spectroscopy of biological materials and, in a planning stage, physico-chemical studies related to the spontaneous synthesis of organic compounds and the origin of life.